Clin. exp. Immunol. (1985) **62,** 753–757.

The relationship between atopy and salivary IgA deficiency in infancy

P. P. VAN ASPEREN, MAREE GLEESON,*† A. S. KEMP, A. W. CRIPPS,* S. B. GERAGHTY,* C. M. MELLIS & R. L. CLANCY*† *Department of Immunology, Royal Alexandra Hospital for Children, Camperdown, *Hunter Immunology Unit, Royal Newcastle Hospital, Newcastle Mater Misericordiae Hospital, Newcastle, and †Faculty of Medicine, University of Newcastle, Newcastle, NSW, Australia*

(Accepted for publication 5 July 1985)

SUMMARY

In a prospective study, infants born to atopic parents had a significantly higher prevalence of salivary IgA deficiency at all ages studied than control infants, and the mean non zero IgA level of the potentially atopic infants was significantly lower at 8 and 12 months than of control infants. Of the infants with atopic parents, the prevalence of IgA deficiency was not significantly greater in those who manifested atopic disease during the study period than in those who did not, but the levels were significantly lower at 4 months.

Keywords IgA deficiency atopy atopic disease

INTRODUCTION

The prevalence of IgA deficiency is increased in atopic populations (Kaufmann & Hobbs, 1970). The observation of a reduced serum IgA in atopic infants at 3 months of age has led to the concept of a 'transient IgA deficiency' which may allow sensitization to occur in early life via an unprotected mucosal surface (Taylor *et al.*, 1973). Alternatively, a deficiency of IgA may reflect an immunoregulatory abnormality leading to both a reduced IgA and excessive IgE production. In order to investigate these possibilities, we have prospectively studied salivary IgA in a group of potentially atopic infants and a control group of randomly selected infants.

MATERIALS AND METHODS

Subjects. Seventy-nine infants born at two major obstetric units in Sydney, New South Wales, with a family history of atopic disease, were followed for 16 months, and 59 of these for a further 4 months. Twenty-six infants had a bi-parental history of atopic disease, 46 a uniparental history and four of the remaining seven had siblings with atopic disease. All parents were tested for atopy by the skin prick method (Pepys, 1972) with histamine 1 mg/ml, a control solution and rye grass, cat fur, and *Dermatophagoides pteronyssinus* allergen extracts (Bencard, Middlesex, UK). Both parents of 33 infants, and one parent of 34 infants reacted to one or more allergens, confirming the high atopic status of the group. All infants were seen by one of us (P. P. van Asperen) every 4 months. On each occasion a history was taken, physical examination and allergen skin tests were performed, and saliva collected. A control group of 129 infants born at a district hospital in Newcastle, New South Wales, was recruited at random and saliva samples collected every 4 months.

Correspondence: P. P. van Asperen, Department of Paediatrics, Westmead Centre, Westmead 2145, NSW, Australia.

Definition of atopy. For the purpose of this study, an atopic infant was defined as an infant who satisfied at least one of the following previouslydescribed criteria (van Asperen *et al.*, 1984, a):

(a) Atopic dermatitis on at least one of the 4-monthly visits; defined as the presence of areas of scaly erythematous puritic dermatitis, primarily involving flexural folds, face, cheeks or areas behind the ears but excluding xeroderma alone.

(b) A history of wheezing on more than one occasion.

(c) The occurrence of an immediate food reaction with urticaria and/or angioedema within 30 min of ingestion.

(d) A positive skin test to one or more of the allergens tested.

Skin tests. Skin tests were performed using the skin prick method (Pepys, 1972) with the following solutions: histamine 1 mg/ml, cow's milk (Hollister Stier, Washington, USA.), egg albumen (Commonwealth Serum Laboratories, Melbourne, Australia), wheat (Commonwealth Scientific & Industrial Research Organization, Sydney, Australia) and *Dermatophagoides pteronyssinus* (Bencard, Middlesex, UK). Reactions were read after 10 min and wheal sizes recorded. The presence of any wheal in an infant was regarded as positive.

Analysis of salivary IgA. Unstimulated saliva was collected according to the method of Ostergaard and Blom (1977). Salivary IgA was measured by electro-immunodiffusion as previously described (Gleeson *et al.*, 1982) with a detection limit of 5 mg/l.

Statistical analysis. The distribution of salivary IgA was non-Gaussian and in many it was not detected. Therefore in the proportion in whom it was detected the mean and standard deviation of logarithimically-transformed non-zero values were used in statistical calculations. Frequencies and means were analysed by χ^2 and *t*-tests; $P<0{\cdot}05$ were considered significant. Sample sizes varied because of missing values.

RESULTS

The proportion of infants in whom salivary IgA was not detected in the potentially atopic cohort was significantly higher than in the control group at all ages (Table 1). The mean non-zero salivary IgA level was significantly lower at 8 and 12 months in the potentially atopic cohort but not at other ages (Fig. 1). In the potentially atopic cohort, there was no significant difference in the number of infants in whom salivary IgA was not detected, at any age, between those with and without clinical evidence of atopy (Table 2). However, the mean non-zero salivary IgA level was significantly lower at 4 months in those infants with clinical atopy (Table 3).

Table 1. Frequency of detection of salivary IgA in the potentially atopic and control cohorts

Age (months)	Group	Salivary IgA detected	Salivary IgA not detected	Probability level
4	Atopic	60	15 (20%)	<0·005
	Control	120	8 (6%)	
8	Atopic	57	20 (26%)	<0·0005
	Control	104	4 (4%)	
12	Atopic	60	15 (20%)	<0·0125
	Control	81	5 (6%)	
16	Atopic	54	11 (17%)	<0·05
	Control	69	4 (5%)	
20	Atopic	34	12 (26%)	<0·0005
	Control	74	1 (1%)	

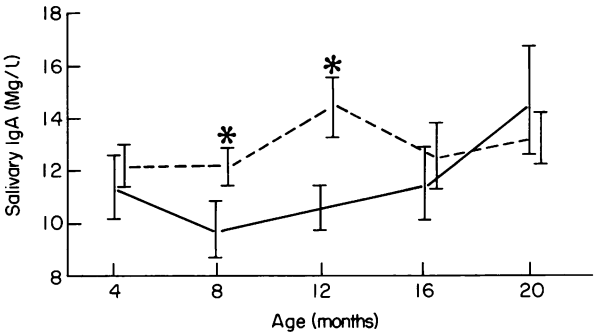

Fig. 1. Comparison of non-zero salivary IgA levels between atopic (———) and control (– – – –) cohorts. *Values for the atopic cohort were significantly less at 8 ($P < 0{\cdot}05$) and 12 ($P < 0{\cdot}0025$) months.

Table 2. Frequency of detection of salivary IgA levels in the potentially atopic cohort.

Age (months)	Group	Salivary IgA detected	Salivary IgA not detected	Probability level
4	Clinical atopy	36	7 (16%)	ns
	No atopy	24	8 (25%)	
8	Clinical atopy	33	11 (25%)	ns
	No atopy	24	9 (27%)	
12	Clinical atopy	37	7 (16%)	ns
	No atopy	23	8 (26%)	
16	Clinical atopy	33	5 (13%)	ns
	No atopy	21	6 (22%)	
20	Clinical atopy	22	7 (24%)	ns
	No atopy	12	5 (29%)	

ns = Not significant.

Table 3. Mean non-zero salivary IgA levels (mg/l) in the potentially atopic cohort

Age (months)	Clinical atopy	No atopy	Probability level
4	9·7	14·2	$< 0{\cdot}05$
8	10·1	9·2	ns
12	11·4	9·4	ns
16	11·1	12·0	ns
20	15·6	12·8	ns

ns = Not significant.

DISCUSSION

The postulated relationship between atopy and IgA deficiency has been based on two lines of evidence. Firstly, an increased prevalence of IgA deficiency in atopic subjects (Kaufmann & Hobbs, 1977) and secondly, the observation of a transient reduction in serum IgA levels at 3 months of age in atopic infants (Taylor *et al.*, 1973; Soothill *et al.*, 1976). Our findings of an increased prevalence of salivary IgA deficiency in a group of potentially atopic infants support these previous observations

extending the association between IgA deficiency and atopy to the mucosal level. This increased prevalence of salivary IgA deficiency may be more relevant than a serum deficiency of IgA, as adult levels of salivary IgA are attained by one month of age (Gleeson *et al.*, 1982) in contrast to serum levels which do not reach adult values until after 12 years of age (Stiehm & Fudenberg, 1966). Furthermore, the mean salivary IgA was lower in the potentially atopic infants compared to the control infants at 8 and 12 months of age, but not at later ages. This finding might explain why studies in older children (Brasher, 1971; Salvaggio *et al.*, 1973; Hobday, Cake & Turner, 1971) and adults (Sigeler & Citran, 1974) have failed to demonstrate differences in secretory IgA levels between atopic and non-atopic patients. However, the prevalence of salivary IgA deficiency in infants from the potentially atopic cohort who developed clinical atopic disease did not differ significantly from those without atopic disease. Furthermore, although infants with atopic disease had a lower level of non-zero salivary IgA at 4 months compared to those without atopic disease, consistent with previous observations on serum IgA (Taylor *et al.*, 1973; Soothill *et al.*, 1976), this level of salivary IgA was equivalent to those without atopic disease at 8 and 12 months.

A number of factors might influence salivary IgA levels. The mode of feeding should be considered as breast feeding might effect IgA levels as well as the development of atopic disease (Burr, 1983) We excluded contamination of salivary specimens with breast milk by screening with a rabbit anti-serum to human colostral whey (Gleeson *et al.*, 1982). In a previous study on salivary IgA levels in infants, we detected no effect of breast feeding on salivary IgA levels between 4 and 12 months of age (Gleeson *et al.*, 1982), nor on the occurrence of salivary IgA deficiency. Finally, in the present study neither 2 or 4 months exclusive breast feeding appeared to influence the development of atopic disease during the period of the study (van Asperen *et al.*, 1984, b). Thus it seems unlikely that the mode of feeding could have influenced our results. Infection should also be considered as it may influence of secretory IgA levels and possibly the development of atopic disease (Frick, German & Mills, 1979). However, in these prospectively studied potentially atopic infants there was no difference in the frequency of respiratory infections between those infants who developed atopic disease and those who did not (unpublished), in keeping with previous observations (Cogswell, Halliday, & Alexander, 1982). Salivary flow rates may have influenced the salivary IgA levels, though collection without stimulation makes this less likely. In addition, it would not account for the difference of prevalence of undetectable salivary IgA between the potentially atopic and control cohorts. The salivary IgA/albumin ratio has been advocated as a more reliable index of salivary IgA content in older children (Salvaggio *et al.*, 1973). Increased mucosal permeability to albumin in early infancy (Gleeson *et al.*, 1982) limit its use in reflecting salivary flow rates in this age group.

The observation of an increased prevalence of secretory IgA deficiency in the potentially atopic cohort may have several explanations. Firstly, IgA deficiency may lead to the development of atopic disease, possibly by failure of antigenic exclusion (Taylor *et al.*, 1973). However, while this and other studies (Kaufmann & Hobbs, 1970; Soothill *et al.*, 1976) have demonstrated that IgA deficiency is more common in an atopic population, atopic disease is not a universal finding in IgA deficient subjects (Hobbs, 1968; Buckley & Dees, 1969; Amman & Hong, 1971; Savilahti, Pelkonen & Visakorpi, 1971; Savilahti & Pelkonen, 1979; Burgio *et al.*, 1980). The prevalence of atopic disease in IgA deficient subjects has varied. Buckley and Dees (1969) reported that 14 (58%) of their 24 subjects with IgA deficiency had atopic disease while Burgio *et al.* (1980) reported that a third of their children with complete IgA deficiency and half of their children with partial IgA deficiency had atopic disease. Neither of these studies defined the clinical parameters of atopic disease they used for diagnosis. On the other hand, Savilahti *et al.* (1971) and Savilahti & Pellonen (1979) reported that two (8%) of 26 patients with complete IgA deficiency had asthma or allergic rhinitis, Amman and Hong (1971) reported three (10%) of 30 patients with IgA deficiency had asthma while Hobbs (1968) reported that only two (5%) of their 39 patients with IgA deficiency had asthma. The observations that only a minority of patients with serum IgA deficiency develop atopic disease and our present findings that the absence of secretory IgA was not associated with the development of atopic disease in early childhood both argue against a direct causal association. Furthermore, it has been suggested that increased antigen exposure may suppress rather than stimulate atopic disease in early childhood (Jarrett, 1984). Alternatively, there may be a common factor which leads to both IgA deficiency and the increased production of IgE and clinical atopy without a causal link between the

two. One possible factor is a defect in immunoregulation and the observation of a significant increase in the median IgE levels in IgA deficient subjects as compared with control subjects and those with other forms of antibody deficiencies (Buckley & Fiscus, 1975) would support this hypothesis. However, the nature of any immunoregulatory defect must remain speculative at this stage.

P. P. van Asperen was supported by a National Health and Medical Research Council (Australia) grant in allergic diseases. We would like to thank the infants and their parents for participating in the study and Mrs Gwen Maharaj and Mrs Barbara Oxlade for secretarial assistance.

REFERENCES

AMMAN, A.J. & HONG, R. (1971) Selective IgA deficiency: Presentation of 30 cases and a review of the literature. *Medicine*, **50,** 223.

BRASHER, G.W. (1971) Salivary IgA in children with atopic disease. *Ann. Allergy*, **19,** 422.

BUCKLEY, R.H. & DEES, S.C. (1969) Correlation of milk precipitins with IgA deficiency. *N. Engl. J. Med.* **281,** 465.

BUCKLEY, R.H. & FISCUS, S.A. (1975) Serum IgD and IgE concentrations in immuno-deficiency diseases. *J. clin. Invest.* **55,** 157.

BURGIO, G.R. DUSE, M., MONATO, V., ASCIONE, D., & NESPOLI, L. (1980) Selective IgA deficiency: Clinical and immunological evaluation of 50 paediatric patients. *Eur. J. Paediatr.* **133,** 101.

BURR, M.L. (1983) Does infant feeding affect the risk of allergy? *Arch. Dis. Child.* **58,** 561.

COGSWELL, J.J., HALLIDAY, D.F. & ALEXANDER, J.R. (1982) Respiratory infection in the first year of life in children at risk of developing atopy. *Br. Med. J.* **284,** 1011.

FRICK, O.L., GERMAN, D.F. & MILLS, J. (1979) Development of allergy in children in association with virus infections. *J. Allergy, clin. Immunol.* **63,** 228.

GLEESON, M., CRIPPS, A.W., CLANCY, R.L., HUSBAND, A.J., HANSLEY, M.J. & LEEDER, S.R. (1982) Ontogency of the secretory immune system in man. *Aust. NZ. J. Med.* **12,** 255.

HOBBS, J.R. (1968) Immune imbalance in dysgammaglobulinaemia type IV. *Lancet*, **i,** 110.

HOBDAY, J.D., CAKE, M. & TURNER, K.J. (1971) A comparison of the immunoglobulines IgA, IgG and IgE in nasal secretions from normal and asthmatic children. *Clin. exp. Immunol.* **9,** 577.

JARRETT, E.E.E. (1977) Activation of IgE regulatory mechanisms by transmucosal absorption of antigen. *Lancet*, **ii,** 223.

JARRETT, E.E.E. (1984) Perinatal influences on IgE responses. *Lancet*, **ii,** 797.

KAUFFMAN, H.S. & HOBBS, J.R. (1970) Immunoglobulin deficiencies in an atopic population. *Lancet*, **ii,** 1061.

OSTERGAARD, P.A. & BLOM, M. (1977) Whole salivary immunoglobulin levels in 60 healthy children determined by a sensitive electroimmunotechnique after prior carbamylation. *J. clin. Chem. clin. Biochem.* **15,** 393.

PEPYS, J. (1972) Laboratory methods in clinical allergy. *Proc. Roy. Soc. Med.* **65,** 271.

SALVAGGIO, J., LOPEZ, M., ARQUEMBOURG, P., WALDMAN, P. & SLY, M. (1973) Salivary, nasal wash and sputum IgA concentrations in atopic and non-atopic individuals. *J. Allergy, clin. Immunol.* **51,** 335.

SAVILAHTI, E., PELKONEN, P. & VISAKORPI, J.K. (1971) IgA deficiency in children. *Arch. Dis. Child.* **46,** 665.

SAVILAHTI, E. & PELKONEN, P. (1979) Clinical findings and intestinal immunoglobulins in children with partial IgA deficiency. *Acta, Paediatr. Scand.* **68,** 513.

SIGELER, D.T.M. & CITRAN, K.M. (1974) Serum and parotid salivary IgA in chronic bronchitis and asthma. *Thorax*, **29,** 313.

SOOTHILL, J.F., STOKES, C.R., TURNER, M.W., NORMAN, A.P. & TAYLER, B. (1976) Predisposing factors and the development of reaginic allergy in infancy. *Clin. Allergy.* **t,** 305.

STIEHM, E.R. & FUDENBERG, H.H. (1966) Serum levels of immune globulins in health and disease: A survey. *Paediatrics.* **37,** 715.

TAYLOR, B., NORMAN, A.P., ORGEL, H.A., STOKES, C.R., TURNER, M.W. & SOOTHILL, J.F. (1973) Transient IgA deficiency and pathogenesis of infantile atopy. *Lancet*, **ii,** 111.

VAN ASPEREN, P.P., KEMP, A.S. & MELLIS, C.M. (1984, a) A prospective study of the clinical manifestations of atopic disease in infancy. *Acta, Paediatr. Scand.* **73,** 80.

VAN ASPEREN, P.P., KEMP, A.S. & MELLIS, C.M. (1984, b) Relationship of diet in the development of atopy in infancy. *Clin. Allergy*, **14,** 525.